Diarylborinic Acids as Efficient Catalysts for Selective Dehydration of Aldols

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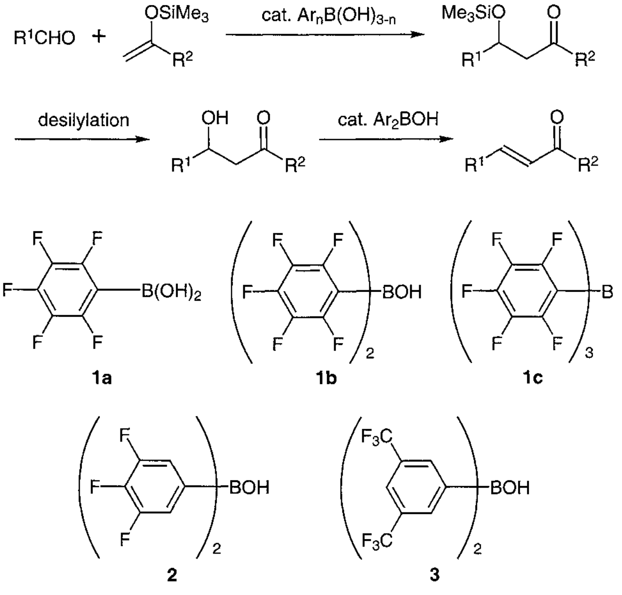
Received 22 January 1997

Abstract: Diarylborinic acids with electron-withdrawing substituents at their aryl groups are efficient Lewis acid catalysts for Mukaiyama aldol condensation and selective dehydration of *anti*-aldols to α,β-enones in the presence of *syn*-aldols. The Lewis acidities of diarylborinic acids are much higher than those of the corresponding arylboronic acids.

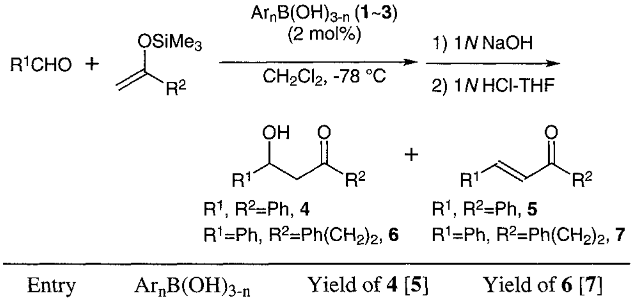
Classical Lewis acids such as $BF_3{\bullet}Et_2O$, $AlCl_3$, $TiCl_4$ and $SnCl_4$ have become popular tools in organic synthesis. In general, these promoters are used stoichiometrically in organic transformations under strictly non-aqueous conditions, since the presence of even a small amount of water causes rapid decomposition or deactivation of the promoters. To obviate some of these inherent problems associated with classical Lewis acids, we have investigated new classes of catalysts derived from traditional metal complexes. For example, we recently demonstrated the potential of tris(pentafluorophenyl)boron (**1c**), which is a convenient, commercially available Lewis acid, as an extremely active catalyst for Mukaiyama aldol condensation,[1a,c] aldol-type condensation of ketene silyl acetals with imines,[1b,c] and stereoselective rearrangement of epoxides.[1d] More recently, its use as a catalyst for addition of Ph_3SiH to carbonyl compounds was reported by Parks and Piers.[2] However, it is difficult to change triarylborons like **1c** into new functional catalysts using synthetic modification. Thus, we have become interested in diarylborinic acids (diarylhydroxyboranes). We describe here the properties of diarylborinic acids with electron-withdrawing substituents at their aryl groups as Lewis acid catalysts in Mukaiyama aldol condensation and subsequent dehydration (Scheme 1).



Scheme 1. Mukaiyama Aldol Condensation and Dehydration of Aldols Catalyzed by Arylboron Compounds

We first examined several diarylborinic acids as Mukaiyama aldol catalysts. The experimental results are summarized in Table 1. As expected, the catalytic activity of bis(pentafluorophenyl)borinic acid (**1b**)[3] was much higher than those of the corresponding arylboronic acid **1a** (entry 1 versus entry 2). Bis(3,4,5-trifluorophenyl)borinic acid (**2**)[5,6] was the most suitable aldol catalyst among the diarylborinic acids **1b**, **2**, and **3**.[5] It is noteworthy that small amounts of *E*-isomeric dehydrated products **5** and **7** were isolated as by-products in the reactions catalyzed by **1b** and **3**. These dehydrated products were not observed in the aldol reaction-step to give β-siloxyketones, but were produced in the subsequent desilylation-step.[7] In contrast, no dehydrated products were isolated in the presence of **1c**, despite the extremely high catalytic activity of **1c**.

Table 1. Mukaiyama Aldol Condensation Catalyzed by Arylboron Compounds [a]



Entry	$Ar_nB(OH)_{3-n}$	Yield of **4** [**5**] (%) [b,c]	Yield of **6** [**7**] (%) [c,d]
1	**1a**	0 [0]	0 [0]
2	**1b**	89 [7]	68 [0]
3	**2**	98 [0]	73 [0]
4	**3**	89 [10]	53 [<5]
5	**1c**	98 [0]	69 [0]

[a] Reaction at -78 °C with 1 mmol of an aldehyde, 1.2 mmol of the trimethylsilyl enol ether derived from acetophenone, 0.02 mmol of an arylboron compound, 2 mL of dichloromethane. The reaction was quenched with 1*N* NaOH, and the crude of β-silyloxyketones was hydrolyzed in 1*N* HCl-THF. [b] Reaction for a period of 1 h. [c] Isolated yield. [d] Reaction for a period of 5.5 h.

Based on the above experimental results, we developed a new and useful method for the dehydration of β-hydroxy carbonyl compounds catalyzed by diarylborinic acids.[8] The results are summarized in Table 2. Initially, solvent effects were investigated in the dehydration of aldol **4** in the presence of 5 mol% of **3** (entries 5~8). We found that this dehydrartion was strongly promoted in THF. Other boron compounds were also examined in THF, and **1b** was found to have a similar catalytic activity (entry 2). In fact, **1b** was superior to **3** for substrate **4**. The dehydration was relatively slow and the retro-aldol reaction occurred in the presence of **1c**, which is a stronger Lewis acid than **1b** (entry 3). *Significant features of these active boron catalysts are that they are strong Lewis acids and possess a hydroxy group on the boron atom.* No dehydration proceeded in the presence of classical BrØnsted acids such as 1*N* HCl and TsOH (entries 9 and 10).

To explore the generality and scope of diarylborinic acid-catalyzed dehydration, some structurally diverse β-hydroxy carbonyl compounds were examined in this reaction (Table 3). In most cases, the reaction proceeded smoothly, and α,β-enones were obtained as *E* isomers in high yields.[9] In the reaction of α-substituted-β-hydroxy carbonyl compounds, α,β-enones were preferentially obtained from *anti*-aldols,

Table 2. Dehydration of Aldol **4** Catalyzed by Arylboron Compounds[a]

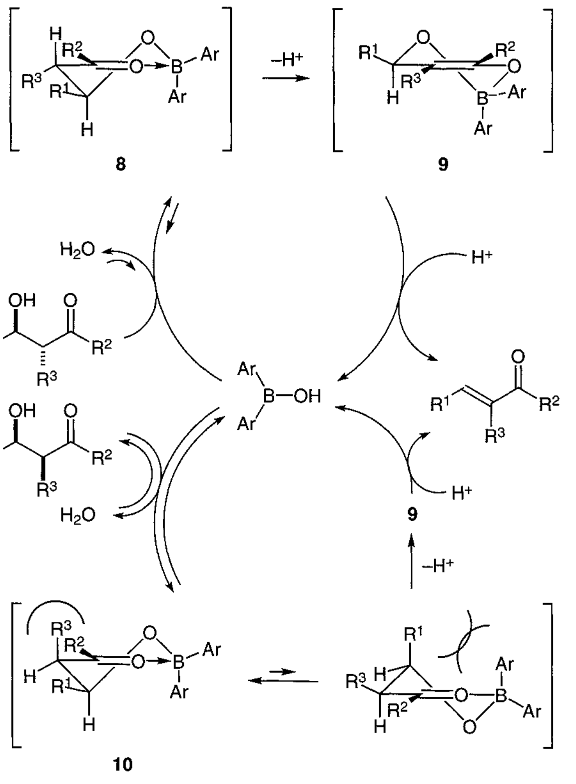
$$\mathbf{4} \xrightarrow[\text{solvents, 17 °C, 2 h}]{\text{Ar}_n\text{B(OH)}_{3-n}\ (\mathbf{1}\sim\mathbf{3})\ (5\ \text{mol\%})} \mathbf{5}$$

Entry	Arylboron Compound	Solvent	Conversion (%)[b]
1	**1a**	THF	0[c]
2	**1b**	THF	100
3	**1c**	THF	26[c]
4	**3**	THF	40[c]
5	**3**	THF	100
6	**3**	Et_2O	81
7	**3**	toluene	2
8	**3**	CH_2Cl_2	0
9	1*N* HCl[d]	THF	0
10	TsOH	THF	0 (<40)[e]

[a] Reaction at 17 °C with 0.2 mmol of **4**, 0.01 mmol of an arylboron compound, and 1 mL of solvents for a period of 2 h, except where noted. [b] Determined by ^{1}H NMR analysis of the crude products. [c] Retro-aldol reaction partially occurred. [d] 1 mL of 1*N* HCl was added in place of arylboron compounds. [e] The conversion (reaction condition: THF, reflux, 4 h) is indicated in parenthesis.

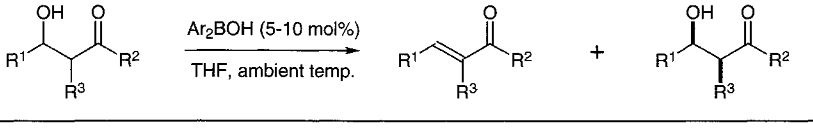
and most of the *syn*-aldols were recovered. *Thus, the present dehydration is a useful and convenient method for isolating pure syn-aldol from syn- and anti-isomeric mixtures.*[11]

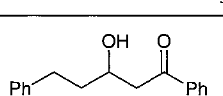
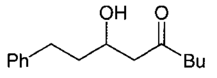
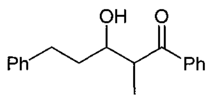
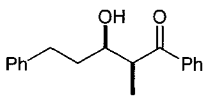
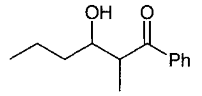
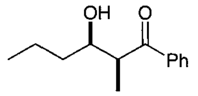
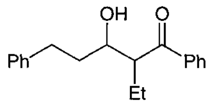
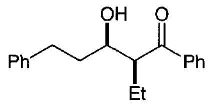
The mechanism we propose to explain the boron-catalyzed dehydration is depicted in Scheme 2. Reaction of the β-hydroxy function with diarylborinic acid would lead to a cyclic intermediate **8**, which should be susceptible to dehydration.[8] Although THF is essential for deprotonation at the α-positions of β-hydroxy carbonyl compounds because its ethereal oxygen is basic, it may facilitate the generation-step of **8** by the ligand-exchange reaction between water and aldols.[12]



Scheme 2. Proposed Mechanism for the Selective Dehydration of *Anti*-Aldols Catalyzed by Diarylborinic Acids

Table 3. Dehydration of β-Hydroxy Carbonyl Compounds Catalyzed by Diarylborinic Acids[a]



Entry	β-Hydroxy Carbonyl Compounds	*syn* : *anti*[b]	Ar_2BOH (mol%)	Time (h)	Conversion[c] (%)	Recovered Aldol (%), *syn* : *anti*[c]
1	 (**6**)		**1b** (5)	3	92	
2			**3** (5)	3	>99	
3			**3** (5)	24	97	
4		71 : 29	**1b** (10)	24	35	 65, >99 : 1
5		83 : 17	**1b** (10)	24	24	 76, >99 : 1
6		54 : 46[d]	**1b** (10)	48	42	 58, 87 : 13[d]

[a] Reaction at ambient temperature with 0.2 mmol of β-hydroxy carbonyl compounds, 0.01 or 0.02 mmol of diarylborinic acids, and 1 mL of THF for several hours. [b] Determined by ^{1}H NMR analysis. [c] Determined by ^{1}H NMR analysis of the crude products. [d] Stereochemistry was not determined.

Subsequently, the transformation to α,β-enones occurs *via* an enolate intermediate **9** derived from the deprotonation of a pseudo-axial α-proton perpendicular to the carbonyl face. The pseudo-equatorial preferences of R^1 and R^3 in **8** formed from an *anti*-aldol lead the α-proton in a pseudo-axial direction. On the other hand, a cyclic intermediate **10** formed from a *syn*-aldol and a diarylborinic acid is thermodynamically less stable than **8**, and the direction of the α-proton is not favorable for deprotonation. Thus, dehydration to (*E*)-α,β-enones selectively occurs for *anti*-aldols.

In summary, we have demonstrated that diarylborinic acids with electron-withdrawing substituents at their aryl groups are highly efficient Lewis acid catalysts of Mukaiyama aldol reaction and subsequent substrate-diastereoselective dehydration. Other synthetic reactions using diarylborinic acids are now underway.

Acknowledgments. H. K. acknowledges a JSPS Fellowship for Japanese Junior Scientists. Tris(pentafluorophenyl)boron was generously donated by Toso-Akuzo Chemical Co., Japan.

References and Notes

(1) (a) Ishihara, K.; Hanaki, N.; Yamamoto, H. *Synlett* **1993**, 577. (b) Ishihara, K.; Funahashi, M.; Hanaki, N.; Miyata, M.; Yamamoto, H. *Synlett* **1994**, 963. (c) Ishihara, K.; Hanaki, N.; Funahashi, M.; Miyata, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1721. (d) Ishihara, K.; Hanaki, N.; Yamamoto, H. *Synlett* **1996**, 721.

(2) Parks, D. J.; Piers, W. E. *J. Am. Chem. Soc.* **1996**, *118*, 9440.

(3) **1b** was prepared by hydrolysis of the known bis(pentafluorophenyl)boron chloride.[4]

(4) Chambers, R. D.; Chivers, T. *J. Chem. Soc.* **1965**, 3933.

(5) Preparation of compounds **2** and **3**: To the corresponding arylmagnesium bromide (2 equiv) was added trimethylborate (1 equiv) at -78 °C, the mixture was stirred at ambient temperature for 2 days. The reaction mixture was poured into ice-cold 1 *M* HCl aq., extracted with CH_2Cl_2 twice, dried over Na_2SO_4, filtered, and concentated *in vacuo*. The crude product was purified by sublimation with bulb-to-bulb distillation apparatus to give the desired diarylborinic acid as a white solid.
2: sublimation (100-150 °C/0.07 mmHg, oven temperature); IR (KBr) 3618, 1613, 1586, 1530, 1425, 1350, 1215, 1071, 1046, 974, 876, 864, 713, 680, 625 cm^{-1}; ^{11}B NMR (96 MHz, C_2D_6SO) δ 9.56; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (t, *J*=7.2 Hz, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) -157, -135. Anal. Calcd for $C_{12}H_5F_6BO$: C, 49.71; H, 1.74. Found: C, 49.66; H, 1.56.
3: sublimation (150-200 °C/0.03 mmHg, oven temperature); IR (KBr) 3350, 1619, 1350, 1140, 970, 911, 845, 714, 683, 646 cm^{-1}; ^{11}B NMR (96 MHz, C_2D_6SO) δ 9.19; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 2H), 8.18 (s, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.7. Anal. Calcd for $C_{16}H_7F_{12}BO$: C, 42.33; H, 1.60. Found: C, 42.20; H, 1.47.

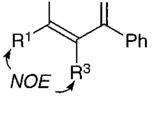
(6) For 3,4,5-trifluorobenzeneboronic acid as an amidation catalyst, see: Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196.

(7) Dehydration of the trimethylsilyl ether of **4** proceeded relatively slowly. The dehydration of the silyl ether is believed to proceed *via* hydrolysis, based on the experimental finding that small amounts of **4** were observed during the dehydration.

(8) For other useful methods for the dehydration of β-hydroxy carbonyl compounds, see: (a) Corey, E. J.; Andersen, N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlattas, I.; Winter, R. E. K. *J. Am. Chem. Soc.* **1968**, *90*, 3245. (b) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310. In most cases, β-hydroxy carbonyl compounds are dehydrated under severe conditions such as heating in the presence of strong acids or bases.

(9) The *E* isomers of α,β-enones obtained in entries 4~6 in Table 3 were assigned by ^1H 2-D NOESY studies at 300 MHz. These results are consistent with the assignments using increments, according to which the resonance of the olefinic proton in *E* isomer is found at higher δ-values.[10]

The chemical shifts of the olefinic protons in ^1H NMR ($CDCl_3$)



R^1=$Ph(CH_2)_2$, R^3=Me: δ 6.29 (Table 3, entry 4)
R^1=Pr, R^3=Me: δ 6.30 (Table 3, entry 5)
R^1=$Ph(CH_2)_2$, R^3=Et: δ 6.16 (Table 3, entry 6)

(10) Matter, U. E.; Pascual, C.; Pretsch, E.; Pross, A.; Simon, W.; Sternhell, S. *Tetrahedron* **1969**, *25*, 691.

(11) It was ascertained by control experiments that dehydrations of *syn*- and *anti*-isomeric aldol mixtures catalyzed by TsOH were not substrate-diastereoselective.

(12) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049.